BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 13, 1951

CONTRIBUTIONS TO THE MATHEMATICAL BIOLOGY OF EXCITATION WITH PARTICULAR EMPHASIS ON CHANGES IN MEMBRANE PERMEABILITY AND ON THRESHOLD PHENOMENA

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Simple chemical reactions of Ca^{++} and K^+ ions with a P^- ion in a membrane are assumed to be causes of changes in permeability of that membrane to K^+ ions. On the basis of such a mechanism a quantative concept of membrane permeability to K^+ ions is defined. The diffusion of K^+ ions through such a membrane is studied mathematically in a simplified version. An applied electrical field as well as the diffusion potential of the K^+ ions are considered to effect the chemical equilibrium constants of the proposed reactions. It is shown that such a system, which can be described by a set of nonlinear differential equations, may have two stable states of equilibrium which are separated by an unstable equilibrium state. As a consequence, such a system may possess a threshold. Estimations of resting potential, threshold—electrical as well as chemical—and of permeability increase, together with that of the corresponding electrical field strength are shown to have the correct order of magnitude. A possible way to derive the one-factor theory from a physical mechanism as considered here is outlined. It is pointed out that the dependence of the thresholds and the permeability changes on several parameters might be calculated on the basis of such a mechanism. As an example it is shown how in principle some of these relations are derived. Furthermore, the time course of excitatory disturbance for different intensities of the initial disturbance are derived theoretically for the case of chemical stimulation. The curves so obtained show a striking similarity in all the characteristic features with the corresponding ones which are obtained experimentally for the case of electrical stimulation of nerve. These results suggest that response to electrical and chemical stimulation is based on a common threshold phenomenon such as considered here. Finally, a more detailed mathematical description, which takes into account explicitly the diffusion of K^+ ions through the membrane for a finite thickness of the membrane is outlined. The equations obtained, which seem to be infeasible of solution at the present time, suggest that it is plausible that relaxation oscillations with a threshold can be derived on the basis of such a mechanism as proposed here. Qualitative agreement with experimental evidence is indicated.

The concept of threshold is a typical bio-mathematical concept and plays a basic role in electrophysiology (see, e.g., Schaefer, 1940) and the mathematical biology of the (central) nervous system (Rashevsky, 1948). Some suggestions as to the quantum-physical nature of this concept were made by A. Bethe (1937) and P. Jordan (1944).

An attempt to derive the all-or-none law on a probabilistic basis was made by H. von Schelling (1944). A formal attempt in connection with subthreshold potentials based on an electrical model of a membrane-element, the resistance of which is assumed to be a nonlinear function of the potential difference across the membrane, was made by B. Katz (1947). Another mechanism which exhibits threshold effects was derived by A. Rapoport (1950) from a probabilistic treatment of neural nets.

I. Tasaki and T. Takeuchi (1941) obtained an action curve from one node. As an estimate of the length of one node we might take (cf., e.g., Engström and Lütky, 1950) as high a value as 3×10^{-3} cm, while the liminal length is of the order of 10^{-1} cm (Rushton, 1937). From these estimates we may infer that propagation along one node is not very likely. The result mentioned above of Tasaki and Takeuchi would then be an example of local excitation without propagation, which still gives an action curve. Furthermore, according to Tasaki (1940), the all-or-none law holds, in general, for excitation of a single node.

One of the postulates of the formal theory of W.A.H. Rushton (1937) underlying much recent experimental work (e.g., Katz, 1937; 1939) corresponds to a local threshold. It is, in fact, assumed in this theory that the local condition of the membrane suddenly changes after the resting charge of the membrane has been altered by a critical amount θ_1. From equation (8) of Rushton's paper (*loc. cit.*), it follows that the liminal length is greater than zero only if the critical value θ_1 is greater than zero. The latter would correspond to a local threshold.

In the formal theory of Katz (*loc. cit.*) a threshold mechanism is discussed for one membrane-element only. This would, therefore, also correspond to a local threshold.

A. M. Weinberg (1942) has pointed out that the only thing which can be concluded from the experimental curves describing the subliminal responses of nerve (Katz, 1937, and others mentioned in Weinberg's paper) is that the subsidence of the excitatory state ε is not described by the usual linear differential equations of the one- or two-factor theories, but should be described by a nonlinear differential equation, in which the time-constant is itself a function of ε. Furthermore, he has pointed out that an interpretation of the deviations from linearity in terms of a "local response" in accordance with Rushton's notion of liminal length (*loc. cit.*; Katz, 1939) is somewhat irrelevant from the strictly phenomenological viewpoint, a physical interpretation of such a nonlinearity being outside the scope of a formal theory. A local threshold is postulated also in the two-factor theory of nerve conduction (Rashevsky, 1948).

In the light of what has been mentioned above, one might believe that it is plausible that a local threshold exists. It is also conceivable that a threshold for the longitudinal gradient of the "polarization" exists (cf. Eichler, 1933; also Katz, 1937, 1939). And it may very well be that those thresholds, if they both exist, are not independent of each other; it is conceivable that the latter threshold might be derived from the former one. We realize that the phenomenon of excitation and propagation is probably described by one, or several, (very difficult) partial differential equations or integrodifferential equations. It would then seem to be artificial to concentrate too much on either the "local" or the "longitudinal" aspect of the problem. However, these exact equations are still unknown at the present time. Therefore we will focus attention here on the local aspect of the process. After what has been said above in relation to work of Tasaki and Takeuchi, Tasaki, Rushton, Katz, and Weinberg, we feel justified in doing this. We would like to remark here, however, that it is conceivable that even if the local response process is essentially a threshold phenomenon, it may appear to be graded (for a different suggestion, see Katz, 1937). This may be due to a combination of several factors. Namely, the stimulation may be "parametric," by which we mean that as a result of the stimulation the conditions are changed with, as a consequence, a change in threshold of the response process. These changes and their consequences may very well be graded. Or, due to experimental techniques, the threshold of local stimulation may be masked either by stimulating too large an area (e.g., by electrical spread or leakage) or by large gradients at the borders of the stimulated area. In this relation the method used by Tasaki, Tasaki and Takeuchi in the papers mentioned above might be preferable. As a matter of fact, as stated above, they obtained an action current in this way from an excited region much shorter than the liminal length, while Tasaki concluded that the all-or-none law holds for such a process.

The importance of relaxation oscillations in relation to the response of tissues to stimuli has been realized for some time. B. van der Pol and J. M. van der Mark (1928) have compared the rhythmic heartbeat with a relaxation oscillation and have pointed out several similarities between the two (e.g., heart block and demultiplication of frequency). A. Fessard (1931) also emphasized the similarity between relaxation oscillations and neural rhythms. Later work of Fessard (1936) and A. Arvanitaki (1938a, b; 1939) also points in the direction of the occurrence of relaxation oscillations in the case of stimulated nerves and myocardium. At this point it might also be of some interest to mention the model experiments of Bethe (1943), O. Schäfer (1943), Bethe and H. Schaefer (1947). D. Auger (1936) found many similarities in this respect between the response of animal and plant cells to stimulation. N. Rashevsky's suggestion for deriving a threshold for relaxation oscillations was elaborated by the author (Karreman, 1949), who was unaware that the theory of these so-called "hard oscillation" cases had already been developed to a certain extent previously (Andronow and Chaikin, 1937; 1949). The problem has been treated recently also by N. Minorsky (1947). These "hard oscillation" cases, with threshold properties, occur, mathematically speaking, if there are at least two limit cycles around a stable singular point, the first one being unstable, the second one stable (Fig. 1).

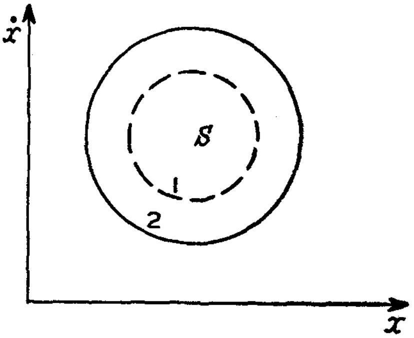

FIGURE 1. Phase plane representing a "hard oscillation." S is a stable singular point, 1 and 2 are limit cycles which are unstable and stable respectively.

The theory of self-excited oscillations has been, to a large extent, based on ideas and work of H. Poincaré (1892). Analytical treatments have also been given by, e.g., van der Pol (1926) and N. Kryloff and N. Bogoliuboff (1937; 1949). It has had many important applications in the case of oscillations of mechanical and electrical systems. In the case of excited muscle and nerve fibers transition through an unstable state or region has been observed (Rushton, 1932; cf. also R. S. Lillie, 1923). Some theoretical approaches in this direction have been made by K. F. Bonhoeffer et al. (1948a through f), together with experimental investigations of the activation of a passive iron wire as a model for the excitation of nerve. R.

S. Lillie had made similar investigations previously (1923, 1924) to get a model for the transmission of nerve impulses. Weinberg (1942) has pointed out the analogy with nonlinear electrical and mechanical systems by constructing a "local phenomenological characteristic" from experimental data (Katz, 1937) on subliminal responses of nerve. In Weinberg's paper several other investigators are quoted who have suggested that the excitation equations are nonlinear.

According to the Membrane Theory proposed by J. Bernstein (1902) the resting potential across the membrane of a nerve or muscle fiber is ascribed to the selective permeability to potassium ions which are present inside the fiber in a concentration which is higher than the normal concentration outside it. K. S. Cole and H. J. Curtis (1938) showed that during activity of Nitella the transverse resistance drops temporarily, suggesting a structural breakdown of the membrane and, as a result, a temporary loss of selective permeability to ions. They (*loc. cit.*; 1939) have also been able to show a close relation between the change of the membrane electromotive force and that of the conductance of the membrane. They consider the sudden changes in those quantities to be connected with the activity which is responsible for the all-or-none law and the initiation and propagation of the nerve impulse. Their results for the squid giant axon correspond to those previously found for Nitella (Cole and Curtis, 1938). There are also suggestions (cf. Schaefer, 1940) that potassium ions effect the structure of the membrane. Furthermore, A. L. Hodgkin (1947) has found that the conductance of the membrane is increased about three-fold when the external potassium concentration is trebled. In addition, there is some evidence that diffusion of potassium ions does play a role in the process of the development of the action potential of giant nerve fibers (Webb and Young, 1940) and that of the giant plant cell Nitella (Osterhout, 1934; Hill and Osterhout, 1934). The latter investigators consider, as a good approximation in the case of Nitella, the diffusion of potassium ions only.* Assuming with Cole and Curtis (1940) that the membrane conductance is a measure of its permeability to ions we see that potassium ions cause an increase of that permeability, presumably (Schaefer, 1940) by causing a so-called "loosening-up" of the membrane; while calcium ions, in general, decrease the ion permeability of the membrane (cf. R. S. Lillie, 1923; Schaefer, 1940). The increase in perme-

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*Very recent investigations (Hodgkin, Huxley, and Katz, 1949), which, unfortunately, came to our attention after the major part of this work had been done, indicate that the increase in the permeability to sodium precedes that of the permeability to potassium in the case of the squid giant nerve fiber during action.

ability at the cathode and the decrease in permeability at the anode might be due (cf. Schaefer, 1940) to this effect of K and Ca if we keep in mind that the concentration of K in the inside of the fiber is greater (and relatively more than that of Ca) than in the outside (Webb and Young, *loc. cit*; von Muralt, 1945) and both ions travel to the cathode from the anode. The importance of structural changes of surface membranes in relation to stimulation had already been stressed by R. S. Lillie (1923). It has been suggested (Heilbrunn, 1943) that during stimulation Ca ions are released from a compound in the cell surface by, e.g., potassium ions. Heilbrunn considers as essential for stimulation a colloid chemical reaction produced by calcium, similar to blood clotting. He and his coworkers have given evidence to that effect in the case of stimulation of lower organisms (for example, Amoeba proteus). In our opinion this scheme is not very likely to account for fast reactions such as occur, e.g., during the stimulation of nerve fibers, since the duration of the action potential is only of the order of milliseconds. We will, therefore, consider a membrane with only one or more layers composed of a calcium compound and will investigate here the diffusion of potassium ions through such a membrane, assuming that the latter are able to react with the calcium compound. According to R. Höber (1945) excitation is a reversible increase of permeability to ions. True enough, Höber considers, with many others, the latter brought about by a transitory dispersion of the colloidal structure of the plasma membrane. These colloidal changes are still hard to treat theoretically, though recent advances in this field (cf. Verwey and Overbeek, 1948) might be very helpful.

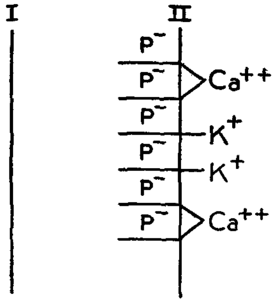

FIGURE 2. Model of a membrane which changes its permeability in accordance with the chemical reaction (1). The numerals I and II represent the inner and outer boundaries of the membrane.

Model of a membrane. We will assume that a compound of Ca,

CaP_2, in which P may represent a fatty acid ion or a lipoid constituent, forms a layer in the membrane. The latter may be mono- or bimolecular (Höber, 1945; Danielli and Davson, 1935) as shown in Figure 2. Potassium ions are supposed to react with this compound (Heilbrunn, 1943) in the following way:

$$CaP_2 + 2K^+ \rightleftarrows Ca^{++} + 2KP. \tag{1}$$

The KP formed by this reaction might be said to produce a "hole" (cf. Höber, 1945; Fleckenstein, 1942), as shown in Figure 2. This concept of hole is, of course, much too simple and much too crude. Instead, the interactions of the Ca^{++}, P^- and K^+ ions should be taken into account in much more detail. Yet it is interesting to see what consequences, particularly quantitative ones, can be drawn from it.

Instead of using the highly oversimplified reaction (1) we will investigate the more appropriate scheme:

$$CaP_2 \rightleftarrows CaP^+ + P^-, \tag{2}$$

$$CaP^+ \rightleftarrows Ca^{++} + P^-, \tag{3}$$

$$P^- + K^+ \rightleftarrows KP, \tag{4}$$

which corresponds to Figure 3.

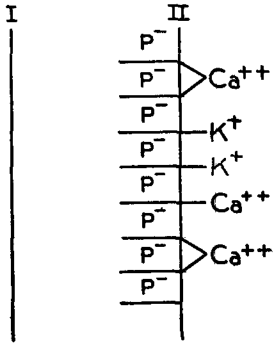

FIGURE 3. Improved model of a membrane which changes its permeability in accordance with the chemical reactions (2), (3), and (4).

We will call the equilibrium constants of these reactions K_1, K_2, and K_3^{-1} respectively. We assume here that we may apply the laws of chemical equilibrium and use the concept of concentration even though we may be dealing with pauci-molecular layers in the membrane. Then we have:

$$K_1 = \frac{(\mathrm{CaP_2})}{(\mathrm{CaP^+})\,(\mathrm{P^-})}, \tag{5}$$

$$K_2 = \frac{(\mathrm{CaP^+})}{(\mathrm{Ca^{++}})\,(\mathrm{P^-})}, \tag{6}$$

$$K_3^{-1} = \frac{(\mathrm{K^+})\,(\mathrm{P^-})}{(\mathrm{KP})}, \tag{7}$$

where parenthesis denote molar concentrations.

Denoting by P_0 the total concentration of $\mathrm{P^-}$ we find:

$$2(\mathrm{CaP_2}) + (\mathrm{CaP^+}) + (\mathrm{KP}) + (\mathrm{P^-}) = P_0\,. \tag{8}$$

We regard the P_0 as determined by metabolic reactions.

Elimination of $(\mathrm{CaP_2})$, $(\mathrm{CaP^+})$ and (KP) from (5), (6), (7) and (8) gives:

$$\begin{aligned} &2K_1K_2(\mathrm{Ca^{++}})\,(\mathrm{P^-})^2 + \{K_2(\mathrm{Ca^{++}}) \\ &+ K_3(\mathrm{K^+}) + 1\}(\mathrm{P^-}) - P_0 = 0\,. \end{aligned} \tag{9}$$

This equation determines $(\mathrm{P^-})$. The two roots of (9) have different signs as can be easily seen. Of course, only the positive root of this equation for $(\mathrm{P^-})$ has a physical meaning.

The first basic assumption we will make is as follows. The permeability h of the membrane to potassium ions is proportional to the number of "holes." The latter number we assume to be proportional to $(\mathrm{KP}) + (\mathrm{P^-})$. Of course, more appropriate (better weighted) combinations of (KP), $(\mathrm{P^-})$, and $(\mathrm{CaP^+})$ might have been chosen. However, a serious difficulty, due to lack of sufficient available data, is to decide at present which combination or function of these concentrations should be taken as a measure of the permeability of the membrane to potassium ions. The different fields of force between the ions should be taken into account, as well as the different masses and, therefore, different moments of inertia, the latter being important for the rotation of the molecules involved.

On the basis of these assumptions we find:

$$a\,h = (\mathrm{KP}) + (\mathrm{P^-}), \tag{10}$$

a being a constant of proportionality.

Through these assumptions, essentially described by equations (2), (3), (4), (8), and (10), the above-mentioned antagonistic influences of $\mathrm{Ca^{++}}$ and $\mathrm{K^+}$ ions on the permeability of membranes is introduced.

Elimination of (KP) from (7) and (10) gives:

$$\alpha h = K_3(\mathrm{K}^+)(\mathrm{P}^-) + (\mathrm{P}^-). \tag{11}$$

Solving (11) for (P^-) we find:

$$(\mathrm{P}^-) = \frac{\alpha h}{K_3(\mathrm{K}^+) + 1}. \tag{12}$$

Introducing (12) into (9) and rearranging leads us to:

$$\frac{2K_1K_2(\mathrm{Ca}^{++})\,\alpha^2}{\{K_3(\mathrm{K}^+) + 1\}^2}h^2 + \frac{K_2(\mathrm{Ca}^{++}) + K_3(\mathrm{K}^+) + 1}{K_3(\mathrm{K}^+) + 1}\alpha h - P_0 = 0. \tag{13}$$

This quadratic equation in h determines h as a function of (K^+) and of (Ca^{++}).

We now introduce the following notations:

$$\begin{aligned} (\mathrm{K}^+) &= c\,,\\ 2K_1K_2(\mathrm{Ca}^{++})\alpha^2 &= a\,,\\ K_3 &= b\,,\\ K_2(\mathrm{Ca}^{++})\alpha &= d\,. \end{aligned} \tag{14}$$

We then can rewrite (13) for $h = h(c)$ as follows:

$$\frac{a}{(bc+1)^2}\left\{h(c)\right\}^2 + \frac{d}{bc+1}h(c) + \alpha h(c) - P_0 = 0. \tag{15}$$

It is easy to see that the function $h(c)$ determined by (15) is

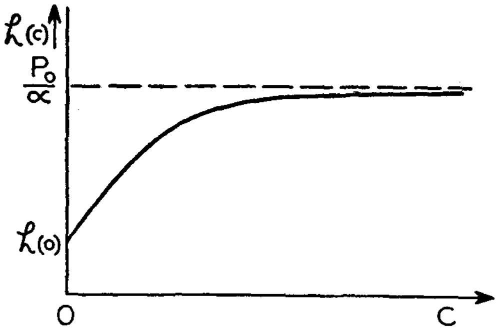

FIGURE 4. Illustration of the relation between the permeability to potassium ions and the concentration of those ions in the membrane on the basis of a mechanism defined by equations (2), (3), (4), (8), and (10).

such that $h(0) > 0$, while $h(c)$ approaches $\frac{P_0}{a}$ if c approaches infinity (which is, of course, beyond the physiological limits). Similarly, $h = \frac{P_0}{a}$ for $(\mathrm{Ca}^{++}) = 0$, implying $a = d = 0$. Furthermore, it can be shown [most easily by differentiation of both sides of (15) with respect to c and using the fact that physiologically $h(c) > 0$] that $h'(c) > 0$ and $h''(c) < 0$ for all positive c [and $h(c)$]. Therefore, plotting $h(c)$ against c we obtain a curve like the one shown in Figure 4.

For later use we will only mention here the dependence of the slope of the curve shown in Figure 4 on the concentration c. It is given by:

$$h'(c) = \frac{\{2ah(c) + df(c)\}\, bh(c)}{\{2ah(c) + df(c) + af^2(c)\}\, f(c)}, \tag{16}$$

$f(c)$ being an abbreviation for

$$f(c) = 1 + bc\,.$$

The diffusion of potassium through the proposed membrane. We will now consider the diffusion of potassium through a membrane of the type outlined in Figure 3. We suppose, as is the case with several living membranes (Höber, 1945), that at one side of the membrane the potassium has the concentration K_1 and at the other side $K_2 \neq K_1$. As is mentioned above, the approximation which considers the diffusion of potassium alone through one or more membranes is the one actually considered by S. E. Hill and W. J. V. Osterhout in a

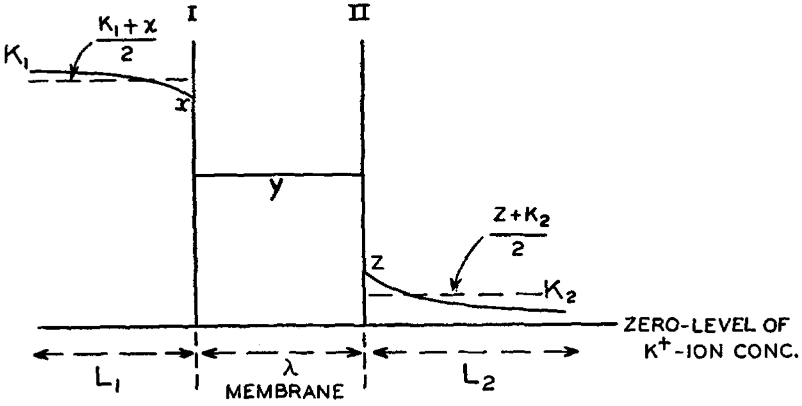

FIGURE 5

long series of papers on the action potentials of the giant plant cell Nitella (e.g., Osterhout, 1934; Hill and Osterhout, 1934; Osterhout and Hill, 1934; 1938). These action potentials have some features in common with those of nerve and muscle fibers.* They also share common features with those of the heart. According to Webb and Young (1940) the diffusion of potassium ions appears to be a principal factor responsible for the development of the action potential. In nerve and muscle fibers, as well as in Nitella cells, the inside concentration K_1 of potassium ions is much greater than their outside concentration K_2 (Höber, 1945). Therefore, we will consider the situation shown in Figure 5.

At both sides of the membrane there are two layers. The first layer, of thickness L_1, is the one in which the diffusion of potassium ions from the high potassium ion concentration K_1 to that (x) just inside the membrane occurs. The other layer, of thickness L_2, is the one in which the diffusion of potassium ions from the concentration (z) just outside the membrane to the low outside concentration K_2 takes place. We will consider the average concentrations in these layers

$$\frac{K_1 + x}{2} \quad \text{and} \quad \frac{z + K_2}{2}$$

respectively, use the approximation method developed by Rashevsky (1948) and take for the permeabilities† of the inside layer I the value $h(x)$; for that of the outside layer II the value $h(y)$. Assuming the chemical reactions to be very fast compared with the diffusion processes, so that they may be considered always to be in equilibrium, we may suppose $h(x)$ and $h(y)$ to be determined by the same type of mechanism as described by equations (2), (3), and (4). Therefore, $h(x)$ and $h(y)$ themselves are determined by an equation of the type (15) with $c = x$ and $c = y$, respectively. Using the approximation method we now find the equations describing the conservation of K^+ ions in both diffusion layers and in the membrane:

$$AL_1 \frac{d\dfrac{K_1 + x}{2}}{dt} = AD_1 \frac{K_1 - x}{L_1} - Ah(x)(x - y), \tag{17}$$

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*Very recently important differences have been pointed out (Hodgkin, 1949).

†Where we speak of permeability in the future we mean the permeability to potassium ions.

$$A\lambda\frac{dy}{dt}=Ah(x)(x-y)-Ah(z)(y-z)\,, \tag{18}$$

$$AL_2\frac{d\dfrac{z+k_2}{2}}{dt}=Ah(z)(y-z)-AD_2\frac{z-K_2}{L_2}\,, \tag{19}$$

A being the cross-section.

Equations (17), (18), and (19) form a set of three simultaneous, nonlinear differential equations. Though the mathematical treatment of this problem in its most simple approximated form leads to this difficult set of differential equations, it is not too difficult to see that the situation might physically correspond to an oscillatory phenomenon occurring after a threshold has been exceeded. Indeed, by raising the external concentration z in Figure 5 the permeability of II is increased since the function $h(z)$ is a monotone increasing function of z. As a consequence, the diffusion of potassium ions through layer II is increased. Therefore, y decreases and z increases initially. With decreasing y the difference between x and y increases so that the diffusion through I increases, lagging behind the increase of diffusion through II. The increased diffusion through I reduces x. Therefore, the difference between K_1 and x is increased. In this model K_1 and K_2 are supposed to be constant (the metabolic process keeping K_1 constantly higher than K_2 is not considered here). The increased difference $K_1 - x$ increases the diffusion in the inside layer which tends to restore the original value of x. At the same time the increase of z increases the diffusion in the outside layer, which decreases z again. Assuming the initial increase of z is large enough (corresponding to a threshold) and the time rates of the various diffusion processes are of the right order of magnitude, we see that it might be possible for the original situation to be restored after practically the whole content of the membrane of potassium ions has been released.

It has been found (Hodgkin and Huxley, 1947) that the charge carried by the potassium ions released in one impulse is about twice the charge on the resting membrane. If one assumes that the latter charge is located in a layer with a thickness of comparable order to that of the membrane, then the above observation is compatible with the mechanism under consideration.

Instead of treating here the set of equations (17), (18), and (19), we will consider first a simplified special case of it, which already shows some interesting features. We assume that the permeability of the membrane is determined by a similar type of mechanism. We again consider a CaP_2 layer as an essential element of the membrane. This compound of CaP_2 is in equilibrium with two complex ions CaP^+ and P^- according to:

$$CaP_2 \rightleftarrows CaP^+ + P^-, \qquad (20)$$

$$CaP^+ \rightleftarrows Ca^{++} + P^-. \qquad (21)$$

The equilibrium constants are, as before,

$$K_1 = \frac{(CaP_2)}{(CaP^+)\,(P^-)} \qquad (22)$$

and

$$K_2 = \frac{(CaP^+)}{(Ca^{++})\,(P^-)}. \qquad (23)$$

We will now consider also some electrical effects. An applied cathode (Fig. 6) will shift the equilibrium of reactions (20) and (21) toward the right-hand side, if we assume that the Ca^{++} ions are bound to relatively immobile P^- ions. This effect is due to the positive charge of the CaP^+ and Ca^{++} ions.

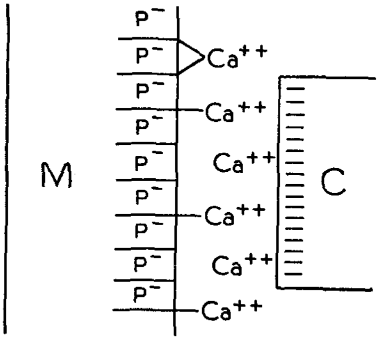

FIGURE 6. Membrane *M* in the neighborhood of an applied cathode *C* illustrating the effect of the attraction of the cathode on the Ca^{++} ions.

We may consider this effect as being due to the attraction of the Ca^{++} ions by the negative electrode. This effect might be expressed by the equation:

$$K_{i,V} = K_{i,0}\, e^{\frac{2\varepsilon}{kT} f V} \qquad (24)$$

in which

V = the electric potential difference across the CaP_2 layer.

$K_{i,V}$ = the equilibrium constant of the ith reaction (20) or (21) ($i = 1, 2$) when the electric potential difference across the CaP_2 layer is V. Similarly for $K_{i,0}$.

ε = the charge of a monovalent ion.

k = the Boltzmann constant.

T = the absolute temperature.

f = a correction factor which expresses the fact that the effective charge of the Ca^{++} ion might be less than 2 and the effective potential difference across the CaP_2 layer might be less than the measured potential difference. Therefore, f may describe the potential drop inside the membrane and across another layer. We will estimate the value of f later and expect it to be less than 1.

We suppose that the electric potential difference V is composed of the applied one (ΔV) and the diffusion potential of potassium. The latter has been assumed here because Osterhout (1949) has shown that it is a good approximation for the resting potential in the case of Nitella (cf. also Fleckenstein, 1942). We then find:

$$V = \frac{RT}{F} \log_e \frac{c_1}{c_2} + (\Delta V), \tag{25}$$

c_1 and c_2 representing the concentrations of K^+ ions at both sides of the layer. Furthermore, it is assumed that the mobility of K^+ ions through the membrane is so much higher than that of any anions (cf. Osterhout, 1949) that the diffusion of the latter does not need to be taken into account in the calculation of the diffusion potential. Introducing (25) into (24) leads to:

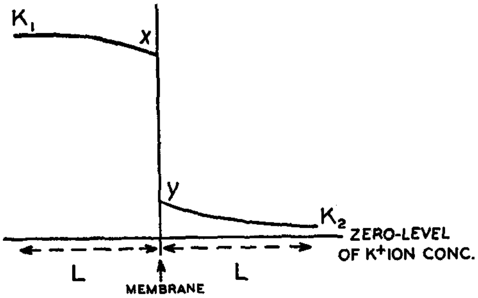

FIGURE 7. Schematic illustration of the concentration levels on both sides of a membrane of negligible thickness.

$$K_{i,V} = K_{i,0} \left(\frac{c_1}{c_2} \right)^{2f} e^{\frac{2\varepsilon}{kT} f(\Delta V)} . \tag{26}$$

As we see, the influence of the electric effects makes the reactions (20) and (21) of higher order.

To simplify matters in another respect, we will treat here first the case of a membrane whose thickness λ may be neglected. Then we have the situation shown in Figure 7.

The thickness of the diffusion layers on both sides of the membrane will be assumed to be the same as well as the diffusion constants of potassium in them. It will be shown, in a more general treatment below (cf. the last part of this paper), that these assumptions do not change anything significantly.

In the same way as above, the diffusion in the two layers next to the membrane with thickness L is found to be described by the following equations:

$$AL \frac{d \frac{K_1 + x}{2}}{dt} = AD \frac{K_1 - x}{L} - Ah(x - y) , \tag{27}$$

$$AL \frac{d \frac{y + K_2}{2}}{dt} = Ah(x - y) - AD \frac{y - K_2}{L} . \tag{28}$$

In these equations the permeability h is considered to be a function of the potassium concentration inside the membrane. It will,

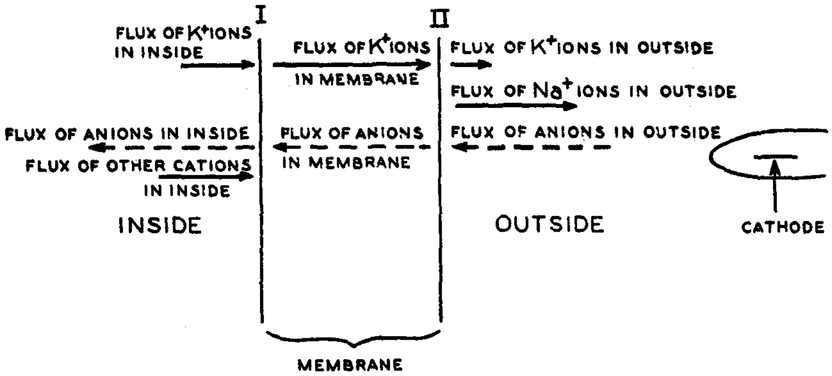

FIGURE 8

therefore, in general, be a function of x and y. However, because x is relatively high, the variations of x are relatively small. In addition, under our assumption that the membrane is permeable only to potassium ions, more of the latter will arrive at the external side of the membrane than leave there. This is because of the continuity of the electric current which inside the membrane is carried by potassium ions and by anions. We have so far neglected the latter for reasons of mathematical simplicity. In the outside layer, however, it is carried for the most part by sodium ions and anions (Fig. 8).

Therefore, the accumulation of K^+ ions will take place at the external side II of the membrane. This is another reason why the permeability is determined to a large extent by y in Figure 7.

However it will be shown later on how the more general case, in which the permeability is also dependent on x, can be treated approximately.

Introducing $h = h(y)$ into the equations (27) and (28) and simplifying the latter equations, we get:

$$\frac{dx}{dt} = \frac{2D}{L^2}(K_1 - x) - \frac{2h(y)}{L}(x - y), \tag{29}$$

$$\frac{dy}{dt} = \frac{2h(y)}{L}(x - y) - \frac{2D}{L^2}(y - K_2). \tag{30}$$

Because h is considered here to be a function of one of the dependent variables, this set of differential equations is also nonlinear. A set of this kind might be considered as a first extension of the usual equations describing diffusion phenomena (including permeability features) with constant diffusion and permeability coefficients, as has been done in most cases up to the present time (Rashevsky, 1948; see also for discussion of some nonlinear diffusion cases).

Addition of the two equations (29) and (30) gives

$$\frac{d(x+y)}{dt} = \frac{2D}{L^2}(K_1 + K_2) - \frac{2D}{L^2}(x + y). \tag{31}$$

The solution of (31) is:

$$x + y = e^{-\frac{2D}{L^2}t}\left\{(x+y)_0 + \int_0^t e^{\frac{2D}{L^2}t}\frac{2D}{L^2}(K_1 + K_2)\,dt\right\},$$

or

$$x + y = (K_1 + K_2) + e^{-\frac{2D}{L^2}t} \{(x + y)_0 - (K_1 + K_2)\}, \qquad (32)$$

$(x + y)_0$ being the initial value of $(x + y)$.

Hence in the steady state (for $t \to \infty$) we have:

$$x + y = K_1 + K_2, \qquad (33)$$

as could have been obtained also directly from (31).

Solving for x from (33), we get:

$$x = (K_1 + K_2) - y. \qquad (34)$$

Subtraction of equation (30) from (29) gives:

$$\frac{d(x-y)}{dt} = \frac{2D}{L^2}(K_1 - K_2) - \frac{2D}{L^2}(x - y) - \frac{4h(y)}{L}(x - y). \qquad (35)$$

To calculate $h(y)$ we will first make the very crude assumption that $f \approx 1$ in (26). For c_1 and c_2 in (26) we take x and y respectively as in Figure 7. Then we find from (26):

$$K_{i,V} = K_{i,0} \left(\frac{x}{y} \right)^2 e^{\frac{2\varepsilon}{kT}(\Delta V)}. \qquad (36)$$

Since

$$y << K_1,$$

and hence

$$y << K_1 + K_2,$$

therefore we may write:

$$x \approx K_1 + K_2. \qquad (37)$$

Hence in this approximation, x may be taken as constant, as could have been concluded from our above considerations in connection with the relatively insignificant variations of x.

We now introduce the following notations:

$$K_1 + K_2 = 2\bar{\Delta}, \qquad (38)$$

$$K_1 - K_2 = 2\bar{\varepsilon}. \qquad (39)$$

Then we find from (36), together with (37) and (38),

$$K_{i,V} = 4K_{i,0}\,\bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\, y^{-2}. \qquad (40)$$

From (22) and (23), in which we now take $K_{i,V}$ instead of K_i, we obtain:

$$(\mathrm{CaP}_2) = K_{1,V}(\mathrm{CaP}^+)(\mathrm{P}^-), \tag{41}$$

$$(\mathrm{CaP}^+) = K_{2,V}(\mathrm{Ca}^{++})(\mathrm{P}^-). \tag{42}$$

Introducing (42) into (41) we find

$$(\mathrm{CaP}_2) = K_{1,V}K_{2,V}(\mathrm{Ca}^{++})(\mathrm{P}^-)^2. \tag{43}$$

We now have the following expression for the reaction system (20) and (21), which is similar to equation (8):

$$2(\mathrm{CaP}_2) + (\mathrm{CaP}^+) + (\mathrm{P}^-) = P_0. \tag{44}$$

Introducing (40) into (41) and (43), and then the latter into (44) we obtain:

$$\begin{aligned} &32K_{1,0}K_{2,0}\,\bar{\Delta}^4\, e^{\frac{4\varepsilon}{kT}(\Delta V)}\,(\mathrm{Ca}^{++})\left(\frac{\mathrm{P}^-}{y^2}\right)^2 \\ &+ 4K_{2,0}\,\bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\,(\mathrm{Ca}^{++})\,\frac{\mathrm{P}^-}{y^2} + (\mathrm{P}^-) - P_0 = 0. \end{aligned} \tag{45}$$

Similar to assumption (10), we assume that in the case of reactions (20)—(21) we have:

$$a\,h = (\mathrm{P}^-). \tag{46}$$

Elimination of (P^-) from (45) and (46) yields the following equation for h:

$$\begin{aligned} &32K_{1,0}K_{2,0}\,\bar{\Delta}^4\, e^{\frac{4\varepsilon}{kT}(\Delta V)}\,(\mathrm{Ca}^{++})a^2\left(\frac{h}{y^2}\right)^2 \\ &+ 4K_{2,0}\,\bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\,(\mathrm{Ca}^{++})a\,\frac{h}{y^2} + a\,h - P_0 = 0. \end{aligned} \tag{47}$$

We will now first show that the term $a\,h$ may be neglected. To do this we have to find plausible estimates for the various parameters. F. C. McLean and A. B. Hastings (1935) find for body fluids:

$$K_{1,0}K_{2,0} \approx 10^3\text{—}10^4\,. \tag{48}$$

Because we might expect $K_{1,0} << K_{2,0}$ (secondary ionizations usually being "weaker" than primary ones), we estimate

$$K_{2,0} \sim 10^2\text{—}10^3. \qquad (49)$$

According to Webb and Young (1940) and R. S. Bear and F. O. Schmidt (1939) we have the following orders of magnitude:

$$(K_1) = 3.10^{-1}\ \mathrm{M/l}\,, \qquad (50)$$

$$(K_2) = 10^{-2}\ \mathrm{M/l}\,. \qquad (51)$$

Taking as an estimate of (Ca^{++}) the value of that concentration in Ringer's solution we find that the order of magnitude is (Fulton-Howell, 1946):

$$(Ca^{++}) \sim 10^{-3}\ \mathrm{M/l}\,. \qquad (52)$$

From (38), (50), and (51) we find:

$$\bar{\Delta} = \frac{K_1 + K_2}{2} = 0.16\ \mathrm{M/l}. \qquad (53)$$

Taking $(\Delta V) = 0$ (no electric field applied), using (49) and (51) and keeping in mind that y is of the order of magnitude of K_2, we find for the coefficient of h in the second term in (47):

$$4.10^2\ (0.16)^2 \cdot 10^{-3}\ (0.01)^{-2}\, a \approx 10^2\, a\,,$$

which is large compared with the coefficient a of h in the third term. We will, therefore, neglect the third term in (47). Equation (47) now takes the form:

$$a_1 \left(\frac{h}{y^2} \right)^2 + b_1 \left(\frac{h}{y^2} \right) - P_0 = 0 \qquad (54)$$

with

$$a_1 = 32 K_{1,0} K_{2,0}\, \bar{\Delta}^4\, e^{\frac{4\varepsilon}{kT}(\Delta V)}\ (Ca^{++})\, a^2 \qquad (55)$$

and

$$b_1 = 4 K_{2,0}\, \bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\ (Ca^{++})\, a\,. \qquad (56)$$

The solution of (54) is given by

$$\frac{h}{y^2} = \frac{-b_1 + \sqrt{b_1^2 + 4a_1 P_0}}{2a_1}, \qquad (57)$$

or

$$h = \beta\, y^2 \qquad (58)$$

with

$$\beta = -\frac{b_1}{2a_1} + \sqrt{\left(-\frac{b_1}{2a_1}\right)^2 + \frac{P_0}{a_1}}. \tag{59}$$

If we again assume as above that the conductance is a measure of the ionic permeability we may compare the theoretically derived result (58) with the observation of Hodgkin (1947) who found that the conductance was increased roughly three-fold when the external potassium concentration was trebled. However, Hodgkin states that there is much scatter in the experimental results and he considers his estimate to be crude. The fact that this investigator also found that the conductance was reduced to about one-half by removal of potassium would suggest that a term h_0, independent of y, should be added to the right-hand side of (58). This term has been omitted in our considerations for reasons of mathematical simplicity. In addition, our formulae (58) and (62) predict a definite dependence of this relation of the conductance and the external potassium concentration on the Ca^{++} ion concentration and on an applied external electrical field. It would be interesting to compare these predictions with experimental data as soon as they are available to obtain some additional ideas for the improvement of this very crude theory.

From (55) and (56) we have

$$-\frac{b_1}{2a_1} = -\frac{1}{16K_{1,0}\,\bar{\Delta}^2\, e^{\frac{2\varepsilon}{kT}(\Delta V)}\,\alpha}; \tag{60}$$

$$\frac{P_0}{a_1} = \frac{P_0}{32K_{1,0}K_{2,0}\,\bar{\Delta}^4\, e^{\frac{4\varepsilon}{kT}(\Delta V)}\,(\mathrm{Ca}^{++})\,\alpha^2}. \tag{61}$$

Substitution of (60) and (61) into (59) leads us to:

$$\beta = \left\{-1 + \sqrt{1 + \frac{8K_1P_0}{K_2(\mathrm{Ca}^{++})}}\right\} \frac{1}{16K_1\,\alpha}\,\frac{e^{-\frac{2\varepsilon}{kT}(\Delta V)}}{\vec{\Delta}^2}, \tag{62}$$

in which the index 0 has been omitted from the ***K***'s. From (58) we see that h plotted as a function of the potassium concentration y gives a parabola (Fig. 9). From (58) and (62) we see that the permeability h decreases with increasing positive applied potential difference (ΔV), while h increases with increasing negative applied potential difference (ΔV). Furthermore, h decreases with increasing (Ca^{++}), while h increases with increasing y, the potassium ion concentration just outside the membrane. All these qualitative conclusions are in agreement with experimental evidence (R. S. Lillie, 1924; Höber, 1945).

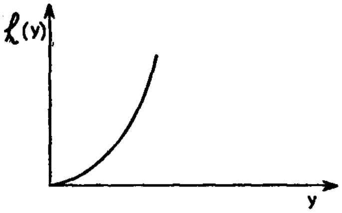

FIGURE 9. Permeability to potassium ions as a function of the potassium concentration just outside the membrane according to equation (58).

Substitution of (39) and (58) into (35) gives

$$\frac{d(x-y)}{dt} = k\,2\,\bar{\varepsilon} - k(x-y) - \frac{4\beta}{L}\,y^2(x-y)\,, \tag{63}$$

where

$$k = \frac{2D}{L^2}. \tag{64}$$

For simplification of notation let us write

$$\frac{4\beta}{L} = \gamma, \tag{65}$$

and introduce as new variables

$$\frac{x+y}{2} = u, \tag{66}$$

$$\frac{x-y}{2} = v, \tag{67}$$

so that

$$x = u + v \tag{68}$$

and

$$y = u - v. \tag{69}$$

From (66), (33) and (38) we then have:

$$u \approx \bar{\Delta}. \tag{70}$$

Introduction of (65), (67), (69) and (70) into (63) yields:

$$\frac{dv}{dt} = k\bar{\varepsilon} - kv - \gamma(\bar{\Delta} - v)^2 v. \tag{71}$$

Rearranging (71) and putting

$$\frac{v}{\bar{\Delta}} = \xi, \tag{72}$$

$$\frac{\bar{\varepsilon}}{\bar{\Delta}} = z, \tag{73}$$

we find:

$$\frac{d\xi}{dt} = k\{z - (1 + \delta)\xi + 2\delta\xi^2 - \delta\xi^3\}, \tag{74}$$

where

$$\delta = \frac{\gamma\Delta^2}{k} \tag{75}$$

is a dimensionless constant, and z now has a new meaning.

Denoting the right-hand side of (74) by $kF(\xi)$, so that

$$F(\xi) \equiv z - (1 + \delta)\xi + 2\delta\xi^2 - \delta\xi^3, \tag{76}$$

we have:

$$\frac{d\xi}{dt} = kF(\xi). \tag{77}$$

Because $x \geqslant 0$ and $y \geqslant 0$, we see from (33), (66) and (67) that v and, therefore, according to (72), ξ, is as great as possible if x is as large as possible and y as small as possible. Physiologically this occurs [$(x + y)/2 = u$ being constant according to (33)] when

$$y = 0. \tag{78}$$

Accordingly, using (66), (70), and (78) we find

$$x = 2\Delta. \tag{79}$$

This means, according to (38), $x = K_1 + K_2 > K_1$.

Therefore, we see from (67), (78), and (79) that the maximum value of v is

$$v = \overline{\Delta}, \tag{80}$$

and that of ξ, according to (72), is

$$\xi = 1. \tag{81}$$

We now find from (76) that

$$\begin{aligned} F(0) &= z > 0, \\ F(1) &= z - 1 < 0. \end{aligned}$$

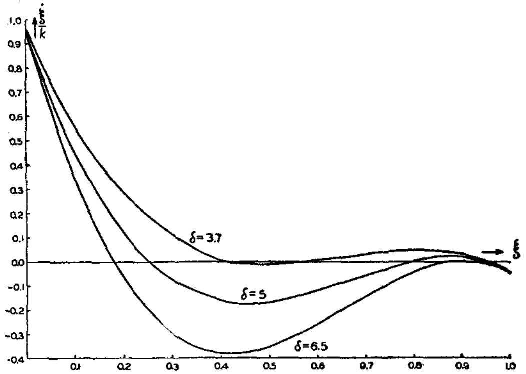

FIGURE 10. Illustration of the relation between $\frac{\dot{\xi}}{k}$ and ξ for $K_1 = 50$ and $K_2 = 1$ mM/l and for several values of δ. The permeability is given by (58) and (62).

A plausible value of z is 0.96. According to (50) and (51), we have $z = 0.94$, while in experiments on Nitella $z = 0.96$ (Osterhout, 1949). The function $F(\xi)$ has been plotted against ξ for $z = 0.96$ and for several values of the parameter δ in Figure 10. If

$$3.65 \leq \delta \leq 6.85, \tag{82}$$

then $F(\xi)$ has three roots in the interval $0 \leq \xi \leq 1$. Therefore, we see that there are three equilibrium values of ξ and hence of x and y also. As it can easily be seen from (74) or from Figure 10, the smallest root of $F(\xi)$ corresponds to a stable equilibrium, the next larger one to an unstable equilibrium, and the largest one again to a stable equilibrium. As an illustration, we find that for $\delta = 5$, $K_1 = 0.050$ M/l, and $K_2 = 0.001$ M/l (Osterhout, 1949), these roots are

$\xi_1 = 0.254$ corresponding to $y_1 = 0.019$ and $x_1 = 0.032$, (83)
$\xi_2 = 0.800$ " " $y_2 = 0.005$ " $x_2 = 0.046$, (84)
$\xi_3 = 0.946$ " " $y_3 = 0.0014$ " $x_3 = 0.050$. (85)

The value y_3 gives the potassium ion concentration in M/l just outside the membrane in the original state. Adding slightly more potassium than $y_2 - y_3 = 0.0036$ (M/l) just outside the membrane does change the equilibrium state into $y_1 = 0.019$ (M/l). As we see here, $y_2 - y_3$ corresponds to a threshold of chemical stimulation through the local addition of potassium outside the membrane. We find here a value of the right order of magnitude (Hill and Osterhout, 1937). Because of the very crude assumptions which we have made, particularly the assumption of $f = 1$ in (26), we can hardly expect more than agreement of the orders of magnitude, and it is not worthwhile to go into the details here. However, at this stage we can estimate the value of f. As we have seen above, increasing the (Ca^{++}) decreases β according to (62) and, therefore, also, according to (65) and (75), δ. As we see from Figure 10 decreasing δ moves the two smaller roots toward each other until they coincide. At the same time the distance between the two larger roots, corresponding to the threshold, increases. For still smaller values of δ than that one which corresponds to the coincidence of the two smallest roots, there remains only the largest root corresponding to the original state. This dependence of the threshold on the (Ca^{++}) might correspond to the experimentally observed increase of threshold (or decreased irritability) upon adding Ca^{++} ions (R. S. Lillie, 1923; Höber, 1945). Also, the original state might be restored (cf. Osterhout, 1933 for a restoration of irritability by adding $CaCl_2$ solution). Adding more Ca^{++} than corresponds to the smallest value of δ, for which there are still three roots, might also lead to Ca narcosis. The quantity β increases with increasing applied negative potential difference, as is seen from (62). Therefore, according to (65) and (75), δ also increases. Hence this mechanism also gives parametric electrical stimulation by an applied cathode. To estimate f we will consider the case in which δ is changed in such a way that starting with the situation $\delta = 3.65$ in which the two smaller roots coincide we arrive at the situation $\delta = 6.85$ in which the two larger roots coincide. The latter corresponds to zero threshold. We have then, from (62),

$$e^{-\frac{2\varepsilon}{kT} f(\Delta V)} = \frac{6.85}{3.65}. \qquad (86)$$

From the known values of ε and k, taking $T = 300°K$, we find:

$$f(\Delta V)_{\mathrm{mV}} = -8\,.$$

Assuming that $(\Delta V)_{\mathrm{mV}} = -10$, which is experimentally of the right order of magnitude (Cole and Curtis, 1940), we find

$$f = 0.8\,. \tag{87}$$

Though higher than we might have expected, we find a value of f which is less than 1 for a reasonable value of the electrical threshold.

Using this value of f we find for the "resting potential" which corresponds to the original state, according to (85), a potential difference of the order

$$58(0.8)\log\frac{50\times 10^{-3}}{14\times 10^{-4}} = 72\,(\mathrm{mV})\,, \tag{88}$$

which is of the right order of magnitude (Osterhout, 1949).

Similarly, we may make an estimate of the "action potential." From equations (83) and (85) we find the value

$$58(0.8)\left(\log\frac{32\times 10^{-3}}{19\times 10^{-3}} - \log\frac{50\times 10^{-3}}{14\times 10^{-4}}\right) = -59\,(\mathrm{mV})\,, \tag{89}$$

which is also of the correct order of magnitude (Hill and Osterhout, 1934). This would correspond to the depolarization of the membrane.

Furthermore, the permeability increase corresponding to the transition from the original state to the final state is, according to (58), (83), and (85),

$$\left(\frac{19\times 10^{-3}}{14\times 10^{-4}}\right)^2 \approx 200\,. \tag{90}$$

This is also the right order of magnitude (Cole and Curtis, 1938). However, it should be realized here that this is only a very crude result; the range of validity of our approximation should be investigated. Particularly, the neglect of the third term in (47) is no longer justified; however, the order of magnitude probably does not change significantly due to this approximation.

It might be interesting to show here a possible way in which the one-factor theory may be obtained from the above considerations.

We shall show this also as an example for the particular case

$\delta = 5$. From the curve in Figure 10, corresponding to this value, we have the equation

$$\dot{\xi} = k(0.96 - 6\xi + 10\xi^2 - 5\xi^3)$$

or

$$\dot{\xi} = -5k(\xi - 0.254)(\xi - 0.800)(\xi - 0.946). \tag{91}$$

We then have for the slope at the value $\xi = 0.946$, corresponding to the original equilibrium state,

$$\left(\frac{d\dot{\xi}}{d\xi}\right)_{\xi=0.946} = -0.5k.$$

Therefore, approximating the curve given by (91) by its tangent at the point $(0.946, 0)$, we have from Taylor's theorem, keeping only terms linear in ξ:

$$\dot{\xi} = \dot{\xi}_{\text{init.}} - 0.5k(\xi - 0.946). \tag{92}$$

The initial value of $\dot{\xi}$, $\dot{\xi}_{\text{init.}}$, due to stimulus or "impulse," is

$$\dot{\xi}_{\text{init.}} = \int_0^t \ddot{\xi}\, dt = C, \tag{93}$$

where C is a constant, which, however, depends on the time course of the stimulus.

Substituting into (92) for ξ its value from (72) and (67), using

$$\dot{\xi} = \frac{\dot{x} - \dot{y}}{2\Delta},$$

and keeping in mind that according to our approximation (33)

$$\dot{x} + \dot{y} = 0,$$

we find:

$$\dot{y} = C_1 - 0.5k(y - 0.0014), \tag{94}$$

where C_1 is proportional to C and 0.0014 M/l is the value of y in the original equilibrium state. From (94) we see that our k turns out to have the order of magnitude of the time factor of the one-factor theory.

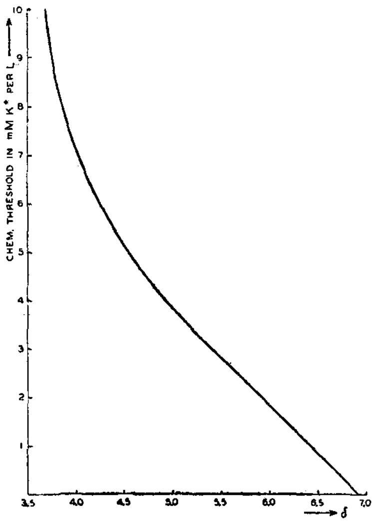

Figure 11. Chemical threshold of (K^+) in mM/l as a function of the parameter δ for the case $K_1 = 50$ and $K_2 = 1$ mM/l.

The threshold can be determined as a function of δ from the curves in Figure 10. The relation obtained is plotted in Figure 11. From this curve and equations (62), (65), and (75) we can obtain the dependence of this (chemical) threshold on the Ca^{++} ion concentration and on the applied (ΔV). Assuming $(\Delta V) = 0$ and $\delta = 3.65$ we obtain in the above outlined way:

(Ca^{++}) in fractions of ($Ca^{++})_n$	Chem. Threshold in mM/l (K^+)
0.285	0.00
0.300	0.50
0.333	1.20
0.400	2.25
0.500	3.50
0.600	4.50
0.667	5.20
0.833	7.20
0.900	8.00
1.000	10.00

This relation between the chemical threshold and (Ca^{++}) is shown in Figure 12 in which the curve for $\delta = 5$ has also been drawn.

In a similar way, which has also been outlined above, we can

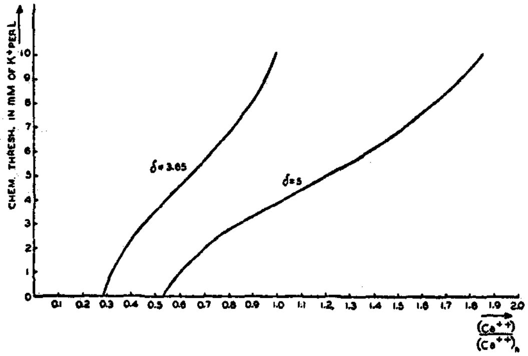

FIGURE 12. Chemical threshold of (K+) in mM/l as a function of $(Ca^{++})/(Ca^{++})_n$ for $K_1 = 50$ and $K_2 = 1$ mM/l.

Two curves are shown, one for the initial value 3.65 for the parameter δ (corresponding to Ca^{++} "narcosis") and the other for the initial value 5 of that parameter. $(Ca^{++})_n$ is the value of (Ca^{++}) corresponding to those values of δ. To simplify the calculations we have chosen for $8K_1P_0 >> K_2$.

calculate the dependence of the threshold of chemical stimulation on the applied field (ΔV) which gives us the following table if we assume the electrical threshold to be —5 mV:

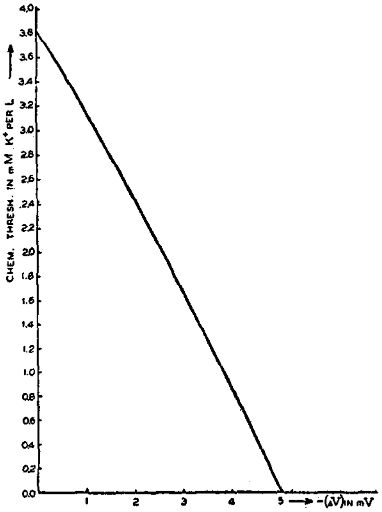

FIGURE 13. Chemical threshold of (K+) in mM/l as a function of an applied voltage for $K_1 = 50$, $K_2 = 1$ mM/l, $\delta_n = 5$. The symbol δ_n denotes the value of the parameter δ when $(\Delta V) = 0$. The electrical threshold is taken to be — 5 mV.

(ΔV) (in mV)	Chem. Threshold in mM/l K^+
0	3.80
—1	3.15
—2	2.42
—3	1.66
—4	0.86
—5	0.00

This relation between the threshold and (ΔV) is shown in Figure 13.

It would be interesting to compare these results with experimental data. As far as we know these are not yet available. The electrical threshold can be expressed as a function of the Ca^{++} ion concentration. From (62), (65), and (75), we find, after some simple rearrangements:

$$\frac{2\varepsilon}{kT} f(\Delta V)_{\substack{\text{thr}\\(\text{Ca}^{++})}} = \frac{2\varepsilon}{kT} f(\Delta V)_{\substack{\text{thr}\\ \text{n}}} + \log_e \frac{-1+\sqrt{1+\dfrac{C}{(\text{Ca}^{++})}}}{-1+\sqrt{1+\dfrac{C}{(\text{Ca}^{++})_{\text{n}}}}}, \qquad (95)$$

in which $(\Delta V)_{\substack{\text{thr}\\(\text{Ca}^{++})}}$ is the electrical threshold corresponding to the particular (Ca^{++}) ion concentration, while $(\Delta V)_{\substack{\text{thr}\\ \text{n}}}$ and $(\text{Ca}^{++})_{\text{n}}$ are the corresponding normal (or, as we may assume, initial) values, and C is a constant equal to

$$\left(\frac{8K_1P_0}{K_2}\right).$$

We can then determine $(\Delta V)_{\substack{\text{thr}\\ \text{n}}}$ from:

$$6.85 = \delta_0\, e^{-\frac{2\varepsilon}{kT} f(\Delta V)_{\substack{\text{thr}\\ \text{n}}}}, \qquad (96)$$

δ_0 being the initial value of δ.

Taking as a plausible value of $\delta_0 = 5$ we find, with $f = 0.8$, $(\Delta V)_{\substack{\text{thr}\\ \text{n}}} = -5$ mV.

We then obtain from (95) the ratio

$$\frac{(\Delta V)_{\substack{\text{thr}\\(\text{Ca}^{++})}}}{(\Delta V)_{\substack{\text{thr}\\ \text{n}}}}$$

as a function of (Ca^{++}). The graph of this function (Fig. 14) may be compared with the corresponding one of F. Brink and others (1946). Though the trend is correct, our range of (Ca^{++}) values in which the threshold changes from 0 to its normal value is much smaller than the one found experimentally. This might perhaps be explained by the fact that local stimulation may be more sensitive than general stimulation or that we have not considered any accommodation effects. The discrepancy is, however, probably due to the crudeness of the theory e.g., the neglect of permeability of Ca^{++} ions and of diffusion potential of Ca^{++} ions.

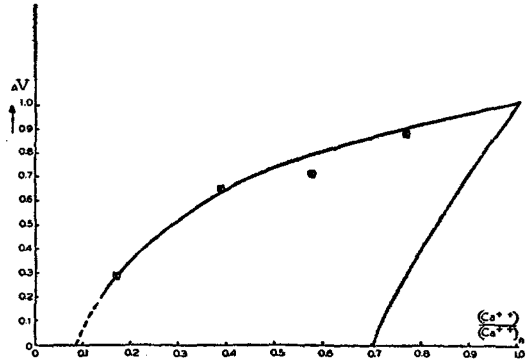

FIGURE 14. Electrical threshold expressed in fractions of its initial value as a function of the ratio $(\text{Ca}^{++})/(\text{Ca}^{++})_n$ for the initial value $\delta_0 = 5$, $K_1 = 50$ mM/l and $K_2 = 1$ mM/l. The initial or normal value $(\text{Ca}^{++})_n$ of (Ca^{++}) corresponds to δ_0 and the normal threshold. In the same graph the experimental values, indicated by x and an experimental curve (Brink and others, 1946) are shown.

Unfortunately, the duration of the "action potential" given by the integral

$$5kt = \int_{0.8}^{0.254} \frac{d\xi}{(\xi - 0.254)(\xi - 0.800)(\xi - 0.946)} \tag{97}$$

for the case $\delta = 5$ is much too large. A slight overshoot of the unstable root 0.8 had to be taken to keep t finite. However, the integral in (97) remains infinite as long as 0.254 is taken as the upper limit. Therefore, the latter also must be slightly shifted. Presumably a recovery process takes place which is superimposed on the considered process and keeps t finite. The infinite value of t, as obtained from (97), is due to the fact that $\dot{\xi} = 0$ at the roots. A similar phenomenon is discussed by Rashevsky (1948, p. 347) in the two-factor theory of conduction.

Another interesting dependence of the threshold is that on K_2, the level of the external potassium concentration. This, however, will be postponed until after a more general analytical treatment is given below. Qualitatively it can be seen already, however, that an increase of K_2, which decreases the quantity

$$z = \frac{K_1 - K_2}{K_1 + K_2},$$

shifts all the curves in Figure 10 toward smaller values of the ordinates. It, also, therefore, decreases the difference of the two largest roots of $F(\xi)$, (the threshold), which is in agreement with experimental evidence (Höber, 1945).

On the basis of the value 0.8 for f we can estimate the electrical field strength corresponding to an applied electrical potential difference of -10 mV. Even if we assume the latter across a distance of 1 Å we find 8×10^5 V/cm for the field strength. This does not compare too unfavorably with an estimate of Osterhout (1934) of 2×10^4 V/mm or more. It would be only slightly worse in this respect for $f = 1$. We see that this model gives some results which are in agreement with experimental facts, at least as far as the order of magnitude is concerned. It is interesting to point out that these results, which give absolute values, were obtained by using the absolute value of the unit electric charge and the Boltzmann constant. However, the fact that the value of f is found to be different from unity indicates that a more general treatment is necessary. The power of y in (58) should be made equal to $nf = p$ instead of 2 where n is the charge of the ion bound to the P^- ion. We have hitherto identified this ion with Ca^{++}. To illustrate this more general treatment and to make some use of it, we proceed as follows. Taking, instead of (58),

$$h = \beta y^p, \tag{98}$$

we obtain, instead of (74), in the same way as before:

$$\dot{\xi} = k\{z - \xi - \beta(1-\xi)^p \xi\}, \tag{99}$$

where the parameters k, z, and β have the same meaning as above, cf. (64), (73), and (62) respectively.

Putting, as before,

$$G(\xi) \equiv \frac{\dot{\xi}}{k} = z - \xi - \beta(1-\xi)^p \xi, \tag{100}$$

we will determine here as functions of p the critical values β_1 and β_2 of β for which the two smaller roots in Figure 15 and the two larger roots respectively coincide. These values of β have given us before, for the case $p = 2$, the order of magnitude of the electrical threshold.

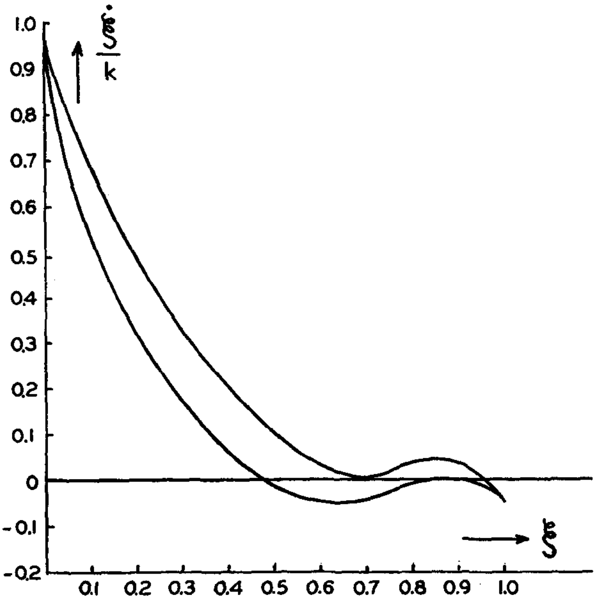

FIGURE 15

Introducing as a new independent variable

$$\eta = 1 - \xi, \tag{101}$$

we have

$$\begin{aligned} G(\xi) &\equiv H(\eta) \equiv z - 1 + \eta - \beta\,\eta^p(1-\eta) \\ &\equiv -\mathbf{e} + \eta - \beta\,\eta^p + \beta\,\eta^{p+1} \end{aligned} \tag{102}$$

in which

$$\mathbf{e} = 1 - z. \tag{103}$$

The curves

$$\dot{\xi} = kG(\xi)$$

or

$$\dot{\eta} = -kH(\eta)$$

are tangent to the ξ or η axis respectively, if:

$$H(\eta) = 0 \tag{104}$$

and

$$H'(\eta) \equiv 1 - p\,\beta\,\eta^{p-1} + (p+1)\beta\,\eta^{p} = 0\,. \tag{105}$$

The latter leads to:

$$\beta = \frac{1}{p\,\eta^{p-1} - (p+1)\eta^{p}}. \tag{106}$$

Substitution of (106) into (104) yields the following quadratic equation in η using (102):

$$p\,\eta^2 - \eta\,\{e(p+1) + (p-1)\} + ep = 0 \tag{107}$$

the solution of which is:

$$\eta_{1,2} = \frac{e(p+1) + (p-1) \pm \sqrt{\{e(p+1) + (p-1)\}^2 - 4ep^2}}{2p}. \tag{108}$$

It can easily be seen that the expression under the sign of the radical,

$$(p+1)^2 e^2 - 2(p^2+1)\,e + (p-1)^2 \geqslant 0$$

if

$$e \leqslant \frac{(p-1)^2}{(p+1)^2}. \tag{109}$$

From (106) and (108) we find the critical values β_1 and β_2 for which we are looking.

In this way the quantities β_1 and β_2 and, therefore, of

$$\frac{\beta_2}{\beta_1} = \frac{\delta_2}{\delta_1},$$

can be expressed as functions of e and p. Because, according to (103), (73), (39), and (38),

$$e = 1 - z = \frac{2K_2}{K_1 + K_2}$$

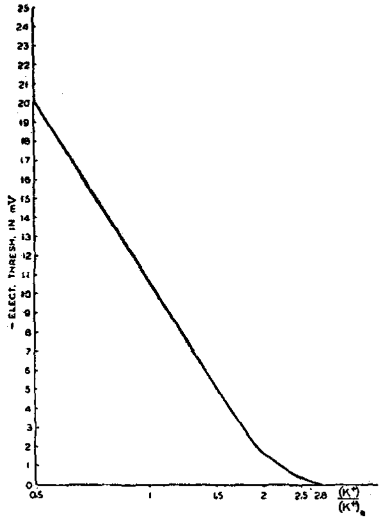

FIGURE 16. The negative of the electrical threshold as a function of $(K_2^+)/(K_2^+)_n$. For reasons of mathematical simplicity it is assumed that the original state corresponds to "narcosis." $K_1 = 50$ mM/l $(K_2^+)_n$ was actually taken in this illustration equal to 1 mM/l. $(K_2^+)/(K_2^+)_n$ has been plotted on a logarithmic scale.

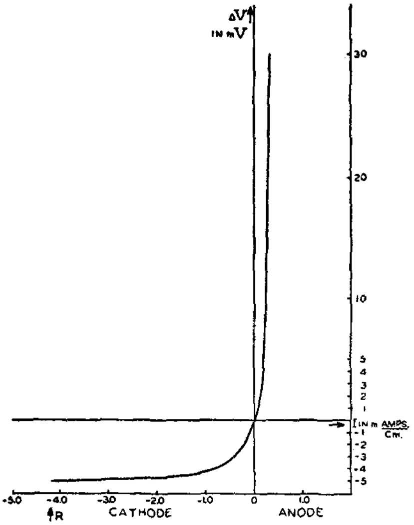

FIGURE 17. Applied potential (ΔV) vs. membrane current intensity I. In order to make these calculations it was necessary to assume that the permeability approached 1/7 of its normal value [when $(\Delta V) = 0$] for small K^+ ion concentration and that in series with the membrane there is an additional resistance 1/12 of that due to the resistance of the normal membrane.

we can calculate in this way $\frac{\delta_2}{\delta_1}$ and, therefore (ΔV) as a function of K_2 for a fixed value of p, e.g., $p = 2$, and for a fixed value of K_1, using the relation

$$e^{-\frac{2\varepsilon}{kT}f(\Delta V)} = \frac{\delta_2}{\delta_1}, \tag{110}$$

obtained from (62) together with (65) and (75). The result of this calculation for $K_1 = 0.050$ M/l is shown in the following table: The calculations were made for a Ca^{++} concentration which corresponds to calcium "narcosis." This particular case was chosen only as an illustration.

K_2 (in M/l)	$-(\Delta V)$ (in mV)
0.0005	20.1
0.0010	10.4
0.0015	5.3
0.0020	1.7
0.0025	0.6
0.0028	0.0

where f is again taken as 0.8.

This relation is shown in Figure 16.*

Furthermore, we can derive from (62) and (58) the permeability h and, therefore, the resistance for negative as well as positive (ΔV) (Fig. 17). This may be compared with Figure 5 of K. S. Cole and H. J. Curtis (1940). The difference may be explained by the fact that we have neglected accommodation effects. On the other hand, it might be interesting to point out here that in principle our formulae predict influences of (Ca^{++}) and K_2 on these rectification curves.

We shall show here how in principle the so-called time-course of the excitatory disturbance and "local non-conducted response" (Katz, 1937) can be obtained from our mechanism. To illustrate this let us again take, only as an example, the curve in Figure 10 for $\delta = 5$, which is given by equation (91).

Denoting by

$$\zeta = -(\xi - 0.946) \tag{111}$$

we find from (91)

---

*The linear relation between the electrical threshold and the external potassium ion concentration for low K_2 has recently been observed by Howard Jenerick (personal communication).

$$-\dot{\zeta} = +5k(0.692 - \zeta)(0.146 - \zeta)\zeta . \qquad (112)$$

The graph of $\dot{\zeta}$ given by (112) against ζ as shown in Figure 18a.

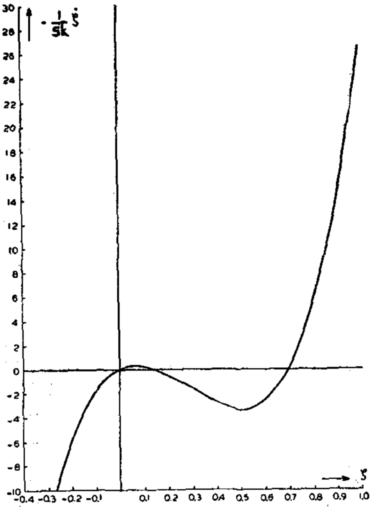

Figure 18a. The "local phenomenological characteristic" for $K_1 = 50$ mM/l, $K_2 = 1$ mM/l and $\delta = 5$.

This corresponds to the "local phenomenological characteristic" of Weinberg (1942). Weinberg's instantaneous time constant, k, is plotted in Figure 18b:

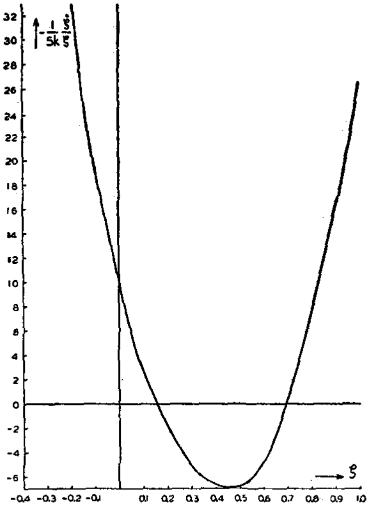

Figure 18b. The "instantaneous time constant" for $K_1 = 50$, $K_2 = 1$ mM/l and $\delta = 5$.

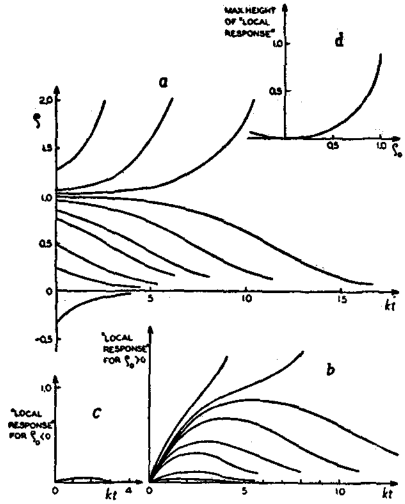

FIGURE 19. a. Graph of standardized excitability $\rho = \dfrac{\zeta}{0.146}$ as a function of kt. b. "Local response" for positive initial disturbance ρ_0 as a function of kt. c. "Local response" for negative initial disturbance ρ_0 as a function of kt. d. Maximum height of the "local response" as a function of ρ_0. This figure is based on $K_1 = 50$ mM/l, $K_2 = 1$ mM/l and $\delta = 5$.

$$k = -\frac{\dot{\zeta}}{\zeta} = 5k(0.146 - \zeta)\,(0.692 - \zeta). \tag{113}$$

Integration of (112) leads us to:

$$kt = -0.46\left\{9.9 \log\frac{\rho}{\rho_0} - 2.65 \log\frac{4.74 - \rho}{4.74 - \rho_0} - 12.5 \log\frac{1 - \rho}{1 - \rho_0}\right\}, \tag{114}$$

where

$$\rho = \frac{\zeta}{0.146}; \qquad \rho_0 = \frac{\zeta_0}{0.146}. \tag{115}$$

It may be well to point out that for a fixed value of $\dfrac{K_1}{K_2}$ the coefficients in (114) are determined by only one parameter δ which was assigned the value 5 in this example.

For several values of ρ_0 the relation between ρ and (kt) given by equation (114) is plotted in Figure 19a. These curves show a striking similarity in all their characteristic features with the curves of Katz (1937, p. 252), which were obtained by electrical shock stimulation of nerve. In Figures 19b, c and d the time-course of the so-called "local response" and the maximum height of the "local response" respectively are plotted, the latter as a function of the stimulus. This should hold for chemical stimulation. Experiments with which these curves could be checked do not seem to exist yet; at least they are unknown to this author. It would, therefore, be very interesting to attempt to obtain these curves by chemical stimulation of nerve or Nitella, which may be easier experimentally due to smaller speed of response. However, in Figure 20 the theoretical curves for $\frac{K_1}{K_2} = 30$ and $\delta = 4$ describing the time course of the chemical excitability are compared with the corresponding curves of Katz (1937) which describe the time course of the electrical excitability. Figure 19c indicates the presence of a "local response" for values of y which are lower than the concentration of potassium in the resting state. These lower concentrations correspond in the case of electrical stimulation to anodal shocks for which no local response is supposed to occur (Katz 1937). Experimental results of Katz (*loc. cit.*) indicate

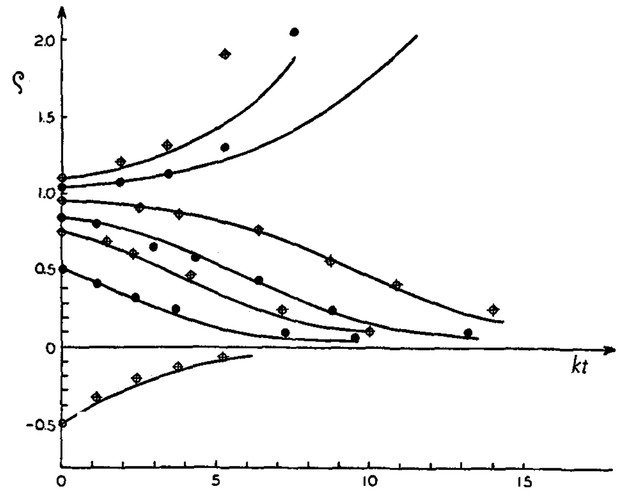

FIGURE 20. Comparison of experimental results (Katz, 1937) with theoretical curves, which were obtained for $\frac{K_1}{K_2} = 30$ and $\delta = 4$ and are described by the equation:

$$kt = -5.32 \log_{10} \frac{\rho}{\rho_0} + 8.45 \log_{10} \frac{1-\rho}{1-\rho_0} - 3.13 \log_{10} \frac{2.7-\rho}{2.7-\rho_0}.$$

the same thing. This corroborates a remark made by Weinberg (1942). As Weinberg (1942) has pointed out so aptly, the only thing which can be concluded from the experimental results is that the phenomenon cannot be described by linear equations. The so-called "local response" which is found for cathodal as well as anodal stimuli is nothing but this deviation from linearity and cannot be interpreted, strictly speaking, on the basis of a phenomenological (Katz, 1937; Rushton, 1937; Weinberg, 1942) theory as had already been pointed out by Weinberg (1942). The theory proposed here, based on a physical mechanism of diffusing potassium ions reacting chemically with a $\mathrm{CaP_2}$ layer, crude as it is, explains these deviations in a plausible way. It predicts that the time constant should be proportional to the square of the intensity of large anodic stimuli. This has not been considered by Weinberg (1942). Actually, the instantaneous time constant of the experimental curves for anodic stimuli (Katz, 1937) do depend on the intensity of those stimuli. However, we have not been able to verify the above-mentioned predicted asymptotic dependence. The reason might be that the experimentally used intensities of the anodic stimuli are not large enough for that purpose.

If the response of the nerve is due to a mechanism such as discussed above, then the so-called "threshold" in Figure 5 of Katz (*loc. cit.*) is no threshold at all. This is seen from our Figure 19b, which is probably more accurate than Katz's figure. Our figure is based on equation (114). The "local response" for $\rho_0 = 0.5$ may not be so slight at all, as shown in our Figure 19b. Therefore, for *this* phenomenon,' relation between maxium height of "local response" and intensity of initial stimulus, there seems to be no threshold. On the basis of our theory the real threshold phenomenon would be more hidden; the "local response" derived from it only appears "graded." If experimental results for chemical stimulation confirmed these predictions, it seems to us that those results, together with those of Katz (1937), would suggest a common underlying physical mechanism for excitation by chemical and electrical stimulation. The physical mechanism proposed here, crude as it is, might then be a plausible one, since it is based on the flow of ions which must occur in some way or another in electrical stimulation and may also occur in chemical stimulation, as shown in this work.

It might be interesting to point out here that from the formulae above a dependence of the curves in Figures 19a, b, c and d on, e.g., $\mathrm{Ca^{++}}$ and K_2 may be derived in principle. As soon as experimental data are available it would be useful to derive those dependences and compare them with the experimental results to obtain some more clues for improving the theory proposed here. There are obviously several possibilities for this.

Thus what may appear to be a graded local response may actually be due to a "local threshold."

Therefore, we would like to end this part of our work with the conclusion that we do not necessarily have to assume that a threshold for a longitudinal gradient [e.g., the longitudinal polarization, cf. Eichler (1933; Katz, 1939)] is the only part of the threshold essential for excitation, but that the latter may very well be due to a local threshold phenomenon as has been assumed in this work.

Outline of an approximate method for treating the diffusion of ions through the membrane. We will in the remaining part of this paper consider a membrane with a finite thickness λ. However, with a rather good approximation, this may be considered to be small compared with L, if we take the plausible value 10^{-4} cm for L, since λ is of the order of 10^{-6} cm (Davson and Danielli, 1943). (See Figure 21.)

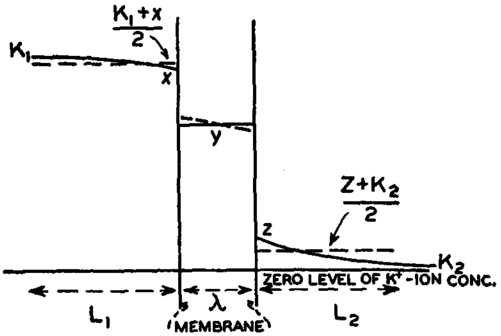

FIGURE 21. Illustration of approximate treatment of the diffusion of K^+ ions through the membrane. The numerals I and II correspond to the vertical "boundaries" in this figure.

To simplify matters we will assume that we may take an average concentration y of the potassium ion in the membrane. Actually we should, of course, consider a gradient of the potassium concentration inside the membrane corresponding to the slanted dotted line between I and II in Figure 21.

Denoting by x and z respectively the concentration of potassium ions at I and II, we find in a similar way as above a description of the system by the following set of differential equations:

$$\frac{L_1}{2}\dot{x} = \frac{D_1}{L_1}(K_1 - x) - h'(x - y), \tag{116}$$

$$\lambda \dot{y} = h'(x - y) - h''(y - z), \tag{117}$$

$$\frac{L_2}{2}\dot{z} = h''(y - z) - \frac{D_2}{L_2}(z - K_2), \tag{118}$$

in which h' and h'' are the permeability to potassium ions of I and II respectively.

We are particularly interested in seeing if it is now possible to get a relaxation oscillation with threshold property if we take a linear dependence of the permeability on the potassium ion concentration. The reason for our interest in relaxation oscillations will be clear from the first part of this paper. The linear dependence of the permeability upon the potassium concentration follows, for sufficiently small potassium ion concentrations, from the mechanism illustrated in Figure 3 and described by the corresponding equations (2)—(16), as shown by Figure 4. The above mentioned experimental relation between the conductance of the membrane and the external potassium ion concentration found by Hodgkin (1947) is also more in line with such a dependence than (58). In addition, it would be of some interest if it could be shown that it might be possible to get a threshold phenomenon with such a linear dependence leading to a concave curve as in Figure 4. In other words, to show that a convex curve is not necessary.

Therefore we will now assume

$$h' = C_1 x\,, \tag{119}$$

$$h'' = C_2 z\,. \tag{120}$$

However, before introducing (119) and (120) into (116), (117), and (118) we will reduce the latter system to two first-order nonlinear differential equations. It would be very advantageous if it were possible to solve the set (116), (117), and (118) using such simple assumptions as in (119) and (120), but we have not been able to do so. The main difficulty is that the set (116), (117), and (118) consists of three nonlinear equations. Such third order systems have been solved, as far as we know, only in a few special cases (Friedrichs, 1946; Rauch, 1950). The reduction to a second-order set mentioned above is done in the following way, using our assumption about the smallness of λ relative to L_1 and L_2. Solving (117) for y gives:

$$y = \frac{h'x + h''z - \lambda \dot{y}}{h' + h''}. \tag{121}$$

Substitution of (121) into (116) and (118) yields, after some elementary rearrangements,

$$\frac{L_1}{2}\dot{x} = \frac{D_1}{L_1}(K_1 - x) - \frac{h'h''}{h' + h''}(x - z) - \frac{h'}{h' + h''}\lambda \dot{y} \tag{122}$$

and

$$\frac{L_2}{2}\dot{z} = \frac{h''h'}{h' + h''}(x - z) - \frac{D_2}{L_2}(z - K_2) - \frac{h''}{h' + h''}\lambda \dot{y}. \tag{123}$$

It is interesting to note that in the latter system the harmonic averages of the permeabilities h' and h'' of the two layers I and II occurs essentially as effective "all-over" permeability of the whole membrane, if we neglect the terms with y because of the smallness of

$$\frac{\lambda}{L_1} \text{ and } \frac{\lambda}{L_2}.$$

Now introducing (119) and (120) into (122) and (123) we find

$$\frac{L_1}{2}\dot{x} = \frac{D_1}{L_1}(K_1 - x) - \frac{C_1C_2xz}{C_1x + C_2z}(x - z) - \lambda\frac{C_1x}{C_1x + C_2z}\dot{y} \tag{124}$$

and

$$\frac{L_2}{2}\dot{z} = \frac{C_1C_2xz}{C_1x + C_2z}(x - z) - \frac{D_2}{L_2}(z - K_2) - \lambda\frac{C_2z}{C_1x + C_2z}\dot{y}. \tag{125}$$

Adding (124) and (125) leads us to:

$$\frac{L_1}{2}\dot{x} + \frac{L_2}{2}\dot{z} = \left(\frac{D_1}{L_1}K_1 + \frac{D_2}{L_2}K_2\right) - \left(\frac{D_1}{L_1}x + \frac{D_2}{L_2}z\right) - \lambda \dot{y}. \tag{126}$$

Subtraction of (125) from (124) leads to

$$\begin{aligned} \frac{L_1}{2}\dot{x} - \frac{L_2}{2}\dot{z} = {} & \left(\frac{D_1}{L_1}K_1 - \frac{D_2}{L_2}K_2\right) - \left(\frac{D_1}{L_1}x - \frac{D_2}{L_2}z\right) \\ & - \frac{2C_1C_2xz}{C_1x + C_2z}(x - z) - \lambda\frac{C_1x - C_2z}{C_1x + C_2z}\dot{y}. \end{aligned} \tag{127}$$

We now introduce the following new variables:

$$\frac{x+z}{2}=\phi, \tag{128}$$

$$\frac{x-z}{2}=\psi, \tag{129}$$

so that

$$x=\phi+\psi \tag{130}$$

$$y=\phi-\psi. \tag{131}$$

We now find, instead of (126) and (127),

$$\frac{L_1+L_2}{2}\dot{\phi}+\frac{L_1-L_2}{2}\dot{\psi}=\left(\frac{D_1}{L_1}K_1+\frac{D_2}{L_2}K_2\right)-\left(\frac{D_1}{L_1}+\frac{D_2}{L_2}\right)\phi -\left(\frac{D_1}{L_1}-\frac{D_2}{L_2}\right)\psi-\lambda\dot{y}, \tag{132}$$

$$\frac{L_1-L_2}{2}\dot{\phi}+\frac{L_1+L_2}{2}\dot{\psi}=\left(\frac{D_1}{L_1}K_1-\frac{D_2}{L_2}K_2\right)-\left(\frac{D_1}{L_1}-\frac{D_2}{L_2}\right)\phi +\left(\frac{D_1}{L_1}+\frac{D_2}{L_2}\right)\psi-\frac{4C_1C_2(\phi^2-\psi^2)\psi}{(C_1+C_2)\phi+(C_1-C_2)\psi} -\lambda\frac{(C_1-C_2)\phi+(C_1+C_2)\psi}{(C_1+C_2)\phi+(C_1-C_2)\psi}\dot{y}. \tag{133}$$

Although unnecessary, we will make the following simplifying assumptions in the remainder of this paper:

$$L_1=L_2=L, \tag{134}$$

$$C_1=C_2=C. \tag{135}$$

Furthermore, for simplification, we shall introduce the following notations:

$$\frac{D_1}{L^2}K_1+\frac{D_2}{L^2}K_2=2\,\Delta_1, \tag{136}$$

$$\frac{D_1}{L^2}K_1-\frac{D_2}{L^2}K_2=2\,\varepsilon_1, \tag{137}$$

$$\frac{D_1}{L^2} = k_1, \tag{138}$$

$$\frac{D_2}{L^2} = k_2, \tag{139}$$

$$k_1 + k_2 = \alpha, \tag{140}$$

$$k_1 - k_2 = \beta, \tag{141}$$

$$\frac{\lambda}{L} = \tau, \tag{142}$$

$$\frac{2C}{L} = \gamma. \tag{143}$$

Introduction of (134)—(143) yields the equations:

$$\dot{\phi} = 2\,\Delta_1 - \alpha\,\phi - \beta\,\psi - \tau\,\dot{y}, \tag{144}$$

$$\dot{\psi} = 2\,\varepsilon_1 - \beta\,\phi - \alpha\,\psi - \gamma\,(\phi^2 - \psi^2)\,\frac{\psi}{\phi} - \tau\,\frac{\psi}{\phi}\,\dot{y}. \tag{145}$$

For the special case considered above—(134) and (135)—we obtain from (121), after introducing into the latter (119) and (120) and differentiating,

$$\lambda\,\dot{y} = \lambda\,\frac{\dot{\phi}\,(\phi^2 - \psi^2) + \dot{\psi}\,2\,\phi\,\psi}{\phi^2}, \tag{146}$$

if we neglect powers of λ higher than the first one.

From (144), (145), and (146) we obtain the following equations linear in $\dot{\phi}$ and $\dot{\psi}$:

$$\left(1 + \tau\,\frac{\phi^2 - \psi^2}{\phi^2}\right)\dot{\phi} + 2\,\tau\,\frac{\psi}{\phi}\,\dot{\psi} = 2\,\Delta_1 - \alpha\,\phi - \beta\,\psi, \tag{147}$$

$$\tau\,\frac{(\phi^2 - \psi^2)\,\psi}{\phi^3}\,\dot{\phi} + \left(1 + 2\,\tau\,\frac{\psi^2}{\phi^2}\right)\dot{\psi} = 2\,\varepsilon_1 - \beta\,\phi - \alpha\,\psi - \gamma\,\frac{(\phi^2 - \psi^2)\,\psi}{\phi}. \tag{148}$$

These equations can be solved for $\dot{\phi}$ and $\dot{\psi}$. The solutions are of the form:

$$\dot{\phi} = F(\phi, \psi, \tau, \alpha, \beta, \gamma, \Delta_1, \varepsilon_1), \tag{149}$$

$$\dot{\psi} = G(\phi, \psi, \tau, \alpha, \beta, \gamma, \Delta_1, \varepsilon_1). \tag{150}$$

In principle we can obtain from the set (149) and (150) a second-order equation e.g. in ψ by elimination of ϕ. To make use of that equation we must introduce drastic approximations. Explicit calculation of F in (149) leads to:

$$\dot{\phi} = \frac{2\Delta_1}{L} - \frac{\alpha}{L}\phi - \frac{\beta}{L}\psi + \tau(.\ .\ .\ .). \tag{151}$$

Neglecting as a zero approximation the terms in τ in this equation, τ being small according to our assumptions, we obtain:

$$\phi = \frac{2\Delta_1}{L} - \frac{\alpha}{L}\phi - \frac{\beta}{L}\psi. \tag{152}$$

Assuming $\beta/\alpha << 1$ we have

$$\dot{\phi} = \frac{2\Delta_1}{L} - \frac{\alpha}{L}\phi, \tag{153}$$

which is similar to (31).

As in (31) we find as the steady state value for ϕ:

$$\phi = \frac{2\Delta_1}{\alpha} = \Delta_2, \tag{154}$$

which we will keep as our first approximation for ϕ.

Introducing

$$\frac{\phi}{\Delta_2} = \eta, \tag{155}$$

$$\frac{\psi}{\Delta_2} = \xi, \tag{156}$$

we find from (154)

$$\eta = 1. \tag{157}$$

We obtain for ξ an equation of the form:

$$\dot{\xi} = k \frac{P_5(\eta\,,\xi)}{P_3(\eta\,,\xi)}, \tag{158}$$

in which $P_5(\eta\,,\xi)$ and $P_3(\eta\,,\xi)$ are polynomials of the order 5 and 3 in ξ respectively.

By differentiating both sides of (158) we obtain

$$\ddot{\xi} - k \frac{\dfrac{\partial P_5}{\partial \xi} P_3 - P_5 \dfrac{\partial P_3}{\partial \xi}}{P_3^2} \dot{\xi} - k \frac{\dfrac{\partial P_5}{\partial \eta} P_3 - P_5 \dfrac{\partial P_3}{\partial \eta}}{P_3^2} \dot{\eta} = 0. \tag{159}$$

Substituting in this equation (157) and an approximation for $\dot{\eta}$ higher than that corresponding to (157), we finally obtain:

$$\ddot{\xi} + \Phi(\xi)\dot{\xi} + \Psi(\xi) = 0\,. \tag{160}$$

At the present stage of development, both experimental and theoretical, it is hardly worthwhile to derive explicitly the expressions for $\Phi(\xi)$ and $\Psi(\xi)$. Though this field of mathematics is momentarily in a rapid rate of progress, as shown by recent work (Andronow and Chaikin, 1937; Minorsky, 1947; Stoker, 1950; Lefshetz, 1950; Kryloff and Bogoliuboff, 1934), the theory for the case in which $\Phi(\xi)$ and $\Psi(\xi)$ are both of higher order in ξ than the first does not seem to be in a form that is ready for application. In a former paper (Karreman, 1949) the author showed (as mentioned in the first part of this paper it had been shown earlier) that in the case in which $\Psi(\xi)$ is proportional to ξ, a relaxation oscillation with threshold can be obtained when $\Phi(\xi)$ is at least of the fourth degree and $\Phi(\xi) = 0$ has at least two appropriate positive and two appropriate negative roots. Although in our present case $\Psi = \Psi(\xi)$ is much more complicated, even in the lowest approximation, we still believe (although we have no proof) that for a self-sustained oscillation it is necessary, in general, for the function $\Phi = \Phi(\xi)$ to be negative for sufficiently long intervals of positive values of ξ and also negative values of ξ. It is interesting now to note that for the special case treated above [see eqs. (134) and (135)] $\Phi(\xi)$ can be shown to have for small τ the following form:

$$\begin{aligned} \Phi(\xi) = k\{ & (1+\mu)(1+2\tau) + 2\tau(z-3\pi)\,\xi \\ & - [3\mu + 2\tau(2+5\mu)]\,\xi^2 + 4\tau\pi\,\xi^3 \\ & + 4\tau\mu\,\xi^4\}/\{1+\tau(1+\xi^2)\}^2\,. \end{aligned} \tag{161}$$

The dimensionless constants are given by

$$\mu = \frac{\gamma \Delta_2}{a}, \tag{162}$$

$$z = \frac{\varepsilon_1}{\Delta_1}, \tag{163}$$

$$\pi = \frac{\beta}{a}, \tag{164}$$

$$k = a, \tag{165}$$

together with (136), (137), (140), and (141).

It is easy to see that $\Phi(\xi) = 0$ has for small τ two positive and two negative roots and has a form similar to that shown in Figure 22, if μ is sufficiently large (z and π being both less than 1, the latter only in absolute value).

Depending on the relative position of the four roots ξ_1, ξ_2, ξ_3, and ξ_4 the situation shown in Figure 22 may lead to the following two cases:

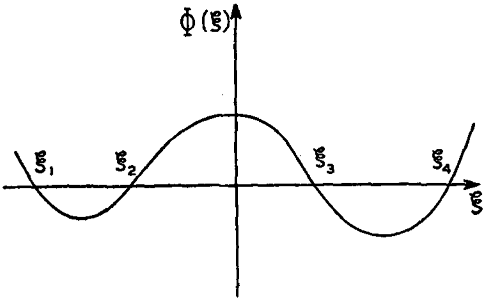

FIGURE 22

1. Only a damped oscillation occurs below a certain "critical" finite disturbance (corresponding to a threshold), if none of the regions of negative damping is reached by it from the original equilibrium state.

2. If the disturbance, above a certain threshold, from the original equilibrium state is such that at least one of the regions has been reached, two things may happen depending upon the circumstances:

a. The regions of negative damping are so far apart that even if self-excited in one of such regions the ξ is damped so much in the intermediate region that it does not reach the other region (cf. Karreman, 1949, where it was shown that in a similar situation; namely, of one region of negative damping, the oscillation was always damped). This would correspond to one spike.

b. The regions of negative damping are sufficiently close so that an undamped threshold oscillation occurs, corresponding to repetitive discharges.

In this way we see that a mechanism such as proposed here might account for a spike as well as an oscillation, both with threshold properties. It is interesting to note that the parameter μ, the relative order of magnitude of which was found to be important above, is determined by the Ca^{++} ion concentration. Rough estimations, taking into account the order of magnitude of the values of α, P_0 and the equilibrium constants K_1 and K_2 in (16) and (14) show that C_i in (119), (120), and (135) is approximately inversely proportional to $\sqrt{(Ca^{++})}$. Because of (143) and (162) the same holds true for μ. We noticed above that μ has to be sufficiently large, particularly if we realize that the four roots discussed above have to be within the physiological limits, which cannot be so easily obtained any longer. Therefore, theoretically we might be led to expect relaxation oscillations for a sufficiently small value of Ca^{++}, which is in agreement with experimental evidence (Brink and others, 1946) in the case of nerve fibers.

Discussion. In a very simple way an attempt has been made to investigate quantitatively the consequences of structural changes in a membrane due to chemical reactions of K^+ ions and a layer consisting of CaP_2 compound through which K^+ ions diffuse. On the basis of these chemical reactions and a "hole" concept, a quantitative definition of the permeability of the membrane, which is supposed to have as an essential element such a CaP_2 layer, to K^+ ions is given. Several possibilities for this have been indicated. One, namely that the permeability of the membrane is proportional to the sum of the concentrations of the formed KP and of the P^-, is elaborated. Equations describing the diffusion of K^+ ions are given with the aid of the approximation method for the case in which the membrane is supposed to have finite thickness and at one or both sides such a CaP_2 layer. In the last part of this paper we have indicated that this explicit consideration of the finite thickness of the membrane leads to nonlinear differential equations which are not amenable to solution at the present time. However there seems to be some indication that they may lead to equations describing relaxation oscillations with threshold properties in qualitative agreement with experimental facts, for instance, as far as the dependence of (Ca^{++}) is concerned. If it is possible in the future to determine the frequency dependence it may be that theoretically observed properties such as frequency demultiplication and dependence of the frequency on (Ca^{++}) can be determined. However since this is a program for the future, a similar mechanism based on the ionization of a CaP_2 layer has been assumed in the central part of this paper as responsible for the determination of the permeability of a membrane whose thickness has been neglected for reasons of mathematical simplicity in the equations describing the diffusion of K^+ ions through it. At the same time some electrical effects due to an applied external electrical field and a "resting potential" across the membrane, using for the latter a diffusion potential of K^+ ions, on the chemical reactions of the CaP_2 layer are taken into account. For mathematical simplicity other electrical effects such as electrical forces on the diffusing K^+ ions, the effects of other ions (e.g., Ca^{++}) on the potential across the membrane, as well as the diffusion of other ions (e.g., Ca^{++} and anions) have been neglected. These omissions, particularly the first two, are thought to be serious shortcomings. On the basis of such a mechanism the permeability of the membrane to K^+ ions is determined. Explicit relations for the dependence of the membrane permeability on an externally applied electrical field, on the Ca^{++} ion concentration, on the average K^+ ion concentration level have been derived in principle. The dependence of the permeability to potassium ions on the K^+ ion concentration is used in the differential equations describing the diffusion of the K^+ ions through the membrane. The latter equations are solved under the assumption that the average K^+ ion concentration has its steady state value. The solution shows threshold properties under certain circumstances. Estimations of "resting potential," threshold (chemical as well as electrical), "action potential," permeability increase, and electrical field across the CaP_2 layer are made and shown to have the correct order of magnitude. A possible way to derive the one-factor theory is outlined. Also, the time course of the excitatory state for various intensities of an initial chemical stimulus has been derived theoretically from the proposed physical mechanism. The curves obtained show all the characteristic features of the corresponding ones for electrical stimulation. It is pointed out, therefore, that these results suggest that response to both electrical and chemical stimulation is based on a common threshold phenomenon as proposed here, which may very well be a local process. Furthermore it is pointed out that the dependence of the latter curves on external parameters such as the Ca^{++} ion and the external K^+ ion concentration may be determined in principle. A more general treatment based on a more general dependence of the permeability to K^+ ions on the local K^+ ion concentration is given and applied to derive the relation between the electrical threshold and the K^+ ion concentration on the outside. Other applications to derive relations between the chemical threshold, the Ca^{++} ion concentration, and the applied electrical potential are made. The dependence of the electrical threshold on the Ca^{++} ion concentrations has been derived theoretically. Comparison of the result obtained with the corresponding experimental result shows that the former gives a more sensitive dependence of the threshold on the Ca^{++} ion concentration. This may be due to the fact that no accommodation effects have been considered theoretically, that the theoretical result refers to local stimulation, and that the threshold derivation neglects the diffusion of Ca^{++} itself as well as the influence of Ca^{++} on the potential difference across the CaP_2 layer considered. Also a current-voltage characteristic has been derived and is compared with the one experimentally obtained. The differences are ascribed to accommodation effects. The possibility of obtaining the dependence of these curves on Ca^{++} ion and external K^+ ion concentration is mentioned. Additional relations which may be predicted on the basis of this theory are the increase in permeability to K^+ ions during activity as a function of the external K^+ ion concentration, of the Ca^{++} ion concentration and of the applied electrical potential (ΔV) (cathodic as well as anodic). These possible extensions all call for more experimentation along these lines.

Though there is a possible manner in which metabolic reactions may be taken into account, namely, through a change in P_0 in equations (8) and (44), they have been neglected above because it was supposed that the metabolic reactions may be assumed to be relatively slow compared with the ionic reactions. Therefore, recovery processes have not been taken into account. It may be worth mentioning here that a mechanism as proposed by E. Eriksson (1949) might perhaps be applied here, the breakdown of the CaP_2 layer as obtained here giving an increase in the P^- anion concentration.

The duration of the development of the action potential could not be determined theoretically on the basis of this mechanism. It seems plausible that the mechanism outlined for obtaining relaxation oscillations might be better in this respect. However, it should be stressed here that the considerations about the relaxation oscillations in the latter part of this paper are only suggestive and might be a starting point for more detailed investigations, complicated as they are. However, they are by no means conclusive and, as will be obvious from the outline given above, they constitute no proof whatsoever. Particularly this holds as long as the physiological limits and, especially, the range of validity of the approximations made have not been determined yet.

Finally, we would like to point out that while we have tried to give an underlying physical picture for changes in permeability to K^+ ions, formally similar mathematical considerations may describe other dependences of the permeability on the K^+ ion concentration or the same, or similar, dependence based on another picture. Furthermore, it might be that similar considerations may apply to ions other than the ion we called the K^+ ion.

Summary.

1. On the basis of the assumption that an essential element of a membrane is a CaP_2 layer, an expression for the permeability of the membrane to K^+ ions diffusing through it and reacting chemically with it has been derived theoretically, taking into account some electrical effects due to the diffusion potential of the K^+ ions and an externally applied electrical potential difference on the chemical reactions.

2. A relation between the permeability to K^+ ions and the concentration of the K^+ ions outside the membrane has been derived, which shows the influence of some factors [Ca^{++} ion concentration, externally applied electrical field (ΔV)] on the former.

3. A threshold of the right order of magnitude is shown to exist for the amount of K^+ ions locally applied to the membrane in order to excite. Also a threshold for parametric electrical stimulation is shown to exist and to have the correct order of magnitude. A way to derive the dependence of the chemical threshold on the Ca^{++} ion concentration has been given. The degree of depolarization of the membrane as calculated here is adequate.

4. Correct orders of magnitude are found on this basis for the resting potential, thresholds, permeability increase, and intensity of the electric field strength across the CaP_2 layer.

5. A possible way to derive the one-factor theory of excitation is indicated.

6. A method is outlined to obtain in principle the time course of the excitatory disturbance and of the local response.

7. A way to obtain relaxation oscillations on the basis of a similar mechanism is outlined.
8. Derivations of other possible relationships are indicated.

It is a great pleasure for the author to express his indebtedness to all members of the Committee on Mathematical Biology for their interest and help during the years he has been studying under their guidance. He wants to thank Professor N. Rashevsky and Prof. H. G. Landau. Professor H. D. Landahl's continued interest, his many helpful, stimulating and encouraging suggestions during the course of preparation of this thesis are gratefully appreciated by the author. The author also wishes to express his great indebtedness to Mrs. Carlton Smith for the very painstaking task of the preparation of this manuscript.

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